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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/542,028	07/12/2005	Nathalie Adje	MERCK-3036	6761

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EXAMINER	
VALENROD, YEVGENY	
ART UNIT	PAPER NUMBER
1621	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,028	ADJE ET AL.	
	Examiner	Art Unit	
	Yevgeny Valenrod	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *23-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/12/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-22 in the reply filed on 2/28/07 is acknowledged. The traversal is on the ground(s) that the PTO has not established an undue burden to examine the full scope of the application. This is not found persuasive because the application is filed as a 371, which is subject to the lack of unity practice. Showing that the groups do not share a special technical feature that makes over the prior art has fulfilled lack of unity requirement.

The requirement is still deemed proper and is therefore made FINAL.

Claims 23-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/28/07.

Objections to the specification

2. The disclosure is objected to because of the following informalities: Continuation data is not included on page one of the specification..

Appropriate correction is required.

3. The disclosure is objected to because of the following informalities: Table E, on page 58 of the disclosure lists identities of S^4 and S^5, however the structure above the

table has variables S^4 and S^6. S^5 is not found in the structure and identities of S^6 are not listed in the table.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-5 and 7-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite the following language "Compounds of...". Such recitation is not consistent with the accepted US practice. **Applicant is advised to amend the claims to recite: "A compound of...".** If one is to follows the claims directions and elect the variables as directed by the definitions in the claim he would arrive at only one compound. Claiming compounds of formula one is therefore indefinite.

5. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "effective amount is indefinite where the claim fails to state the function which is to be rendered effective. In re Fredriksen, 203. USPQ 35 (CCPA 1954).

6. Claims 16 and 17 provide for the use of a compound according to formula 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 16 and 17 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

In order to advance the prosecution of the instant application examiner will treat claims 16 and 17 as "method of preparing a medicament" claims.

7. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-17 recite: "Pharmaceutically acceptable derivatives". The claim is indefinite because the structure and scope of the said derivatives is unclear. The specification fails to define the said term.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-12 and 14-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using or making the compounds of formula I in which W = XL-CO_2R, **does not reasonably provide enablement for using or making the compounds in which W = -X-L-Tet.** The specification does not provide reasonable directions with respect to making and using the compounds where W includes a tetrazole group. Compounds that were prepared represent the scope of compounds with W = XL-CO_2R. Not a single compound in tables A-H (pages 43-72) or of those depicted on pages 74-93 contained a tetrazole group. Only one compound was tested for pharmacological activity (pages 36-37) and that compound also had the COOR containing W. The specification does not enable any skilled pharmacologist or physician to use the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546.

a) The only disclosed utility of the compounds or compositions of the instant invention is in activation of chimeric protein PPAR. Determining if any particular claimed compounds with a

tetrazole group would be active would require synthesis of the compound and subjecting it to testing with Applicants' PPAR activation assay. Considering the large number of compounds to be made this is a large quantity of experimentation. b) The direction concerning the tetrazole containing compounds is found in line 10, page 3, which merely defines W as optionally containing a tetrazole group. c) In the instant case none of the working examples describing preparation or method of using the claimed compounds contain a tetrazole group.

d) The nature of the invention is activation of chimeric protein PPAR and treatment of human diseases with Applicants' compounds. This involves physiological activity. The nature of the invention requires an understanding of the PPAR receptors, the binding activity of small ligands to that receptor, and the ability of those compounds to activate PPAR receptors. In view of the unpredictability of receptor binding activity and claimed divergent substituents with varied polarity, size, and polarisability, the skilled physician would indeed question the inclusion tetrazole groups to commensurate in scope with these claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

e) The state of the art is detailed knowledge of the PPAR receptor is lacking. No X-ray structure of the receptor is known and the structural requirements of ligands to this receptor are poorly understood. The single compound exemplified by the applicant in PPAR receptor activation is a carboxylic acid, which has different physical properties from a tetrazole. A carboxylic acid is by acidic, while tetrazole is basic. There is no reasonable basis for the assumption that the COOR and Tet groups will share the same biological properties. The two groups are different and there is no basis in the prior art for assuming in the non-predictable art

of pharmacology that structurally dissimilar compounds will have similar activity, *In re Surrey* 151 USPQ 724.

f) The artisan using Applicants' invention to treat diseases with the claimed compounds would be a physician with a MD degree and several years of experience. He would be unaware of how to predict *a priori* how a changing a COOH group will effect biological activity. g) Physiological activity, is well-known to be unpredictable, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). h) The breadth of the claims includes all of millions of compounds of formula (I). Thus, the scope is very broad. The specific compounds made are not adequately representative of the compounds embraced by the extensive Markush groups instantly claimed.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

9. Claims 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for activating PPAR receptor with selected compounds, does not reasonably provide enablement for treatment or **prevention** of dislipidemia, atherosclerosis or diabetes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

(A) The breadth of the claims;
(B) The nature of the invention;
(C)The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

Claims 14-17 are drawn to pharmaceutical compositions and a method for preparing pharmaceutical compositions for treatment or prevention of dislipidemia, atherosclerosis or diabetes using a compound of formula (I).

The state of the prior art

Although there are art recognized treatments for dislipidemia, atherosclerosis or diabetes, the examiner notes that the art does not recognize preventive therapeutic agents for said diseases. Applicants are invited to provide evidence to the contrary. In any event, the examiner notes that there is no art provided of record, evidence set forth in the disclosure, or correlation establishing some nexus to support preventive administration or therapy between the art and the instant disclosure to support the alleged disease preventing applicability the pharmaceutical compositions of the instant invention.

The level of one of ordinary skill

The skilled artisan in this field is that of an MD and/or a PhD skilled in the development and treatment of dislipidemia, atherosclerosis or diabetes.

The level of predictability in the art

The examiner acknowledges the probability and predictability that the instantly claimed compounds will activate the PPAR receptor. There is not seen sufficient data to substantiate the assertion that dislipidemia, atherosclerosis or diabetes may be treated or prevented by the compounds of the instant invention. One skilled in this art would not predict from the disclosure provided that dislipidemia, atherosclerosis or diabetes can be treated or prevented using the pharmaceutical compositions of the instant disclosure

The amount of direction provided by the inventor.

The instant specification is not seen to provide adequate guidance, which would

allow the skilled artisan to extrapolate from the same to establish enablement for the treatment or prevention of dislipidemia, atherosclerosis or diabetes. There is not seen guidance as to how the skilled artisan would formulate the requisite active agents and use it in methods for the prevention of either of the claimed diseases.

There is not seen sufficient guidance, which would teach the skilled artisan how to administer, said active agents in methods for treating or preventing dislipidemia, atherosclerosis or diabetes. Activating the PPAR receptor seems to be the limit of what is enabled by the specification.

The existence of working examples

There are no working examples of treating or preventing disease provided in the specification.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the treatment or prevention of any disease or conditions and the skilled artisan would not extrapolate preventive efficacy from the compounds and compositions instantly claimed. Nor is this data alone recognized in the art, as sufficient data to assert compounds with a specific activity would be expected to treat or prevent dislipidemia, atherosclerosis or diabetes.

Claim Rejections - 35 USC § 102

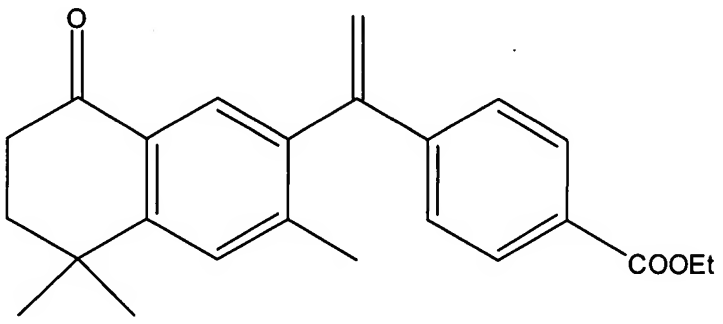
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

10. Claims 1-4, 8 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by Iotzova et al. (US 6,713,515)

Iotzova et al disclose the following compound (column 19, lines 55-65).



The above structure anticipates the compound of claims 1-4, 8 and 12.

Conclusion

Claims 1-30 are pending.

Claims 23-30 are withdrawn.

Claims 1-23 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yevgeny Valenrod whose telephone number is 571-272-9049. The examiner can normally be reached on 8:30am-5:00pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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